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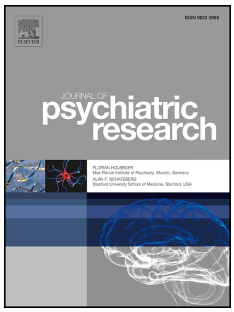

Smaller hippocampal volume in current but not in past depression in comparison to healthy controls: Minor evidence from an older adults sample

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SMALLER HIPPOCAMPAL VOLUME IN CURRENT BUT NOT IN PAST DEPRESSION IN COMPARISON TO HEALTHY CONTROLS: MINOR EVIDENCE FROM AN OLDER ADULTS SAMPLE

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Abstract

Background: Structural neuroimaging studies revealed a consistent pattern of volumetric reductions in both hippocampus (HC) and anterior cingulate cortex (ACC) of individuals with major depressive episode(s) (MDE). This study investigated HC and ACC volume differences in currently depressed individuals (n=150) and individuals with a past lifetime MDE history (n=79) versus healthy controls (n=287). Methods: Non-demented individuals were recruited from a cohort of community-dwelling older adults (ESPRIT study). T1-weighted magnetic resonance images and FreeSurfer Software (automated method) were used. Concerning HC, a manual method of measurement dividing HC into head, body, and tail was also used. General Linear Model was applied adjusting for covariates. Results: Current depression was associated with lower left posterior HC volume, using manual measurement, in comparison to healthy status. However, when we slightly changed sub-group inclusion criteria, results did not survive to correction for multiple comparisons. Conclusions: The finding of lower left posterior HC volume in currently depressed individuals but not in those with a past MDE compared to healthy controls could be related to brain neuroplasticity. Additionally, our results may suggest manual measures to be more sensitive than automated methods.

1. Introduction

According to the World Health Organization, the overall prevalence rate of depressive disorders among older adults ranges from 8 to 20% in the community and up to 37% in primary care (World Health Organization, 2001). Recurrent and chronic major depression is associated with high levels of morbidity and functional impairment (McMahon, 2012). Duration of depression appears to be associated with the extent of global cerebral gray matter change (Lampe, 2003). Structural magnetic resonance imaging (MRI) has been widely used to examine the neuro-structural correlates of depression, in young and elderly populations (Schweitzer, 2001). Meta-analyses of volumetric MRI studies in patients with unipolar depression in comparison with healthy controls have shown volume reductions in the hippocampus (HC) (Campbell, 2004; McKinnon, 2009; Videbech, 2004), the subgenual cortex (Bora, 2012), the amygdala (Hamilton, 2008), the putamen and the caudate nucleus (Koolschijn, 2009), and the right cingulate cortex (Arnone, 2012). The most frequently observed regions of atrophy are the HC, the anterior cingulate cortex (ACC), the prefrontal cortices, the striatum, the amygdala (Du, 2014) and the thalamus (Andreescu, 2008). Among them two limbic structures, the HC and the ACC, seem particularly consistent (Ballmaier, 2004; Steffens, 2000). In particular, HC volume reduction has been repeatedly reported in neuroimaging studies of depressed patients (Campbell, 2014; Malykhin, 2015; Schmaal, 2015; Y. I. Sheline, 1996), including older adults (Ballmaier, 2008; Hickie, 2005; Lloyd, 2004; O'Brien, 2004; Y. I. Sheline, 1996; Steffens, 2000). This reduction could be due to stress, through increased glucocorticoid release which in turn suppresses adult neurogenesis in the dentate gyrus (a HC sub-region) eventually promoting onset of a depressive episode (Eker, 2010; Jacobs, 2000; Sapolsky, 1986). However, HC volume reduction in late life depression (LLD) may also be linked to neurodegenerative disorders, like Alzheimer's disease, in an early or pre-clinical stage (de Flores, 2015). ACC volumes as well seem to decrease in major depressive disorder (MDD) in adulthood (Arnone, 2012; Bora, 2012) but also in LLD (Ballmaier, 2004; Gunning, 2009). This region may play a key role in functions disrupted in depression in older adults as it is connected to brain structures that regulate mood, emotional valence of thought and autonomic and visceral responses (George S. Alexopoulos, 2008).

Brain volume changes due to depression in older adults may be modified by a number of confounding factors. First, female gender (Mulsant, 1999) and past history of depression seem

to increase the risk of LLD (Cole, 2014). Second, magnitude of brain volume reduction has been associated with the severity of the depressive episode (Lorenzetti, 2009; Vakili, 2000). Third, longitudinal studies have shown that cardiovascular risk factors pertaining to the metabolic syndrome increase the risk of LLD (George S. Alexopoulos, 2005; Krishnan, 2002; Laks, 2010; Reaven, 1988). Finally, antidepressant use reduces time to recovery (G. S. Alexopoulos, 1996) and induces brain plasticity especially in prefrontal cortex, ACC, and medial temporal areas (Bellani, 2011).

In order to further understand the differences between currently depressed individuals and persons with past major depressive episode (MDE), who may have recovered in terms of brain atrophy, we investigated the volume differences in the HC and ACC in a general population sample of French older adults. The aim of the present study was to compare HC and ACC volumes in older adults with current or past depression versus healthy controls. To this end we focused on regional reconstruction and segmentation of both regions obtained through FreeSurfer image analysis suite (automated method). Manual HC volume estimation was also undertaken. We hypothesized that HC and ACC volumes would be reduced in depressed older adults controlling for potential confounders, such as gender, metabolic syndrome and antidepressant use.

2. Materials and methods

2.1 Sample

We used data from a prospective study of psychiatric disorders in older adults' community dwellers (the "Enquête de Santé Psychologique – Risques, Incidence et Traitement", or ESPRIT study). In this project, 1863 subjects aged 65 and over were randomly recruited from the 15 electoral rolls of Montpellier district (South of France) between March 1999 and February 2001 (Ritchie, 2004). Participants underwent clinical, biological and neuroimaging assessment administered by trained staff at the Gui de Chauliac Neurology Hospital of Montpellier. Ethical approval was obtained by the ethics committee and written informed consent was collected from all the participants. For the current study, we selected individuals aged ≤ 80 with available MRI imaging data, specifically of estimated HC, ACC and total intracranial volumes (n=661). We then excluded participants with a diagnosis of dementia

(n=15), with missing baseline Mini International Neuropsychiatric Interview (MINI) data (n=16), and with MINI diagnosis other than depression (n=114). A total of 516 individuals were finally retained (see Figure 1 for the flow chart).

2.2 Assessment

Participants completed a standardized interview covering socio-demographic characteristics along with a general health questionnaire about medical history, medications, current alcohol consumption, and tobacco use. Psychiatric diagnoses, including current and lifetime MDE, were assessed using the Mini International Neuropsychiatric Interview (MINI; French version 5.00), validated in the general population and providing DSM-IV diagnoses (Sheehan, 1998). The MINI was administered by trained interviewers (nurses and psychologists) and positive cases were reviewed by a clinical panel of psychiatrists. The Centre for Epidemiologic Studies - Depression Scale (CES-D) (Radloff, 1977) was used to assess the severity of depressive symptoms. A standardized neurological examination, based on the International Classification of Diseases (ICD-10) criteria (World Health Organization, 1992), was used for the diagnosis of dementia. Preliminary diagnosis of dementia was made by a neurologist and validated by an independent national panel of neurologists to obtain consensus.

2.3 Study groups

In older adults, clinically significant depressive symptomatology does not always correspond to the criteria for major depression of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Büchtemann, 2012), although it has similar consequences on well-being and functioning. As one definition alone (categorical versus dimensional) does not adequately capture the current late life depression construct, we based our current depression assessment on the three following criteria: 1) a diagnosis of current MDE at the MINI (onset within the past two weeks) according to the DSM-IV criteria, and/or 2) a CES-D cutoff score ≥16 to account for subsyndromal depressive symptomatology, the clinical significance of which, among older primary care patients, has been demonstrated and which poses substantially elevated risk of persistent depressive symptoms and worsening into major depression (Lyness, 2009), and/or 3) current antidepressant treatment according to the medications' record. While recognizing that in few cases antidepressants could have been prescribed for other reasons (e.g., anxiety or insomnia), we considered that this group could not be excluded as the subjects were likely not to show depressive symptomatology any longer due to the treatment,

but they could still manifest underlying physiological changes.. Identified current depressive older adults were n=150. Past depression was determined by the presence of MDE history at the MINI according to DSM-IV criteria and no current late life depression (to avoid overlapping between the groups). Identified past MDE older adults were n=79. Healthy controls were n=287, they had no past MDE or current late life depression or any other psychiatric disorder screened with the MINI. They had a CESD<15 and no antidepressant use.

2.4 Other measures

Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria (Grundy, 2005). Details of procedures have been previously described (Akbaraly, 2011; Carriere, 2014).

2.5 Imaging analyses

Anatomical scans were acquired in the period 1999-2001. A 1.5 T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighted sequence for volumetric estimations (TR=12, TE=2.8, IT=600, matrix size=256×256, pixel spacing=0.9375×0.9375 mm, NEX=1, slice thickness=1.0 mm).

2.5.1 Automated measurements for HC and ACC

Regional reconstruction and segmentation was performed with the FreeSurfer, version 6.0, image analysis suite (http://surfer.nmr.mgh.harvard.edu/). This contains several stages, the first of which comprised the reconstruction of the cortical surface (Dale, 1999). Normalized intensity images were created, corrected for the variations in intensity due to magnetic field inhomogeneity. Voxels beyond the cerebral cortex, namely the skull, were then removed before segmentation initiated. Segmentation is based on the geometric structure where grey and white matter interface, and subsequently separates the left and right hemispheres as well as cortical from subcortical structures. The resulting cortical volume is covered into a triangular tessellation and deformed to more accurately represent grey and white matter interface as well as the pial surface. Once the cortex has been reconstructed, this volume is registered to a spherical atlas (B. Fischl, SerenoDale, 1999; B. Fischl, Sereno, Tootell, , 1999) and parcellated into regions based on the sulcal and gyral structures (Desikan, 2006; Bruce

Fischl, 2004). Each T1-weighted scan is segmented into cortical and subcortical regions in each hemisphere. Data were then exported into SPSS for analysis (the output of FreeSurfer, mm^3 volumes for each region, was in .dat format and then imported into SPSS).

2.5.2 Manual HC measurements

HC ROIs were manually outlined on consecutive coronal slices and verified from axial and sagittal orientations (Maller, 2007). The anterior tip of the HC until the slice before the opening of the crus of the fornix (CF) was measured as the HC head and body and included the subiculum, CA1–(4) areas, and dentate gyrus (DG), as described by Watson et al. (Watson, 1997), and the HC tail was measured from the slice immediately posterior to that which represented the last slice according to the Watson protocol. The internal structure of the HC tail is the same as in the head and the body, whereby the cornu ammonis has an analogous structure throughout, as does the gyrus dentatus. From the coronal perspective, measuring the HC until the CF represents the part of the tail which coincides with the coronal section of the pulvinar (which is situated in a supero-medial position). Voluminous choroidal plexuses occupy portions of this region, hence care was taken to exclude them laterally from volumetric estimates. The HC was then followed posteriorly. On initial slices, the tail appears bulgy as an ovoid mass of gray matter on the infero-medial part of the lateral ventricle, and more posteriorly it lies flattened on the superior surface of the parahippocampal gyrus. The tail was outlined until the fasciolar gyrus becomes the subsplenium gyrus curving around the postero-inferior margin of the splenium. The superior border was easy to differentiate from the crus of the fornix. The medial and inferior limits were also easily drawn because of the contrast between gray/white matter. Relevant images from standard atlases were referred to in order to ensure a consistent reference to the boundaries and relevant landmarks for these slices of HC. All HC volumes are presented in mm^3.

2.5.3 Intra-rater and inter-rater reliability for HC measurements

HC outlines were traced by two trained researchers blind to the study hypotheses, group assignment and subjects' identity. The reliability of the HC measurements was assessed using a formula to calculate the intra- and inter-class correlations (intra HC, inter HC) that presumes random selection of raters. The two researchers (J.M. and C.M.) each retraced five MRI images, which were randomly selected among the images previously traced, and five images which belonged to the group previously traced by the other researcher. Intra-HC was 0.942

for JM and 0.970 for CM. Inter-HC was 0.939. All these values are well within acceptable limits.

2.5.4 Brain volume

Total brain volume (gray plus white matter) and total intracranial volume (total brain volume plus cerebrospinal fluid volume) were computed for each subject using the 'segment' m-file of the SPM5 software (Wellcome Department of Cognitive Neurology, UK). All outputs were manually inspected to ensure accurate and valid data.

2.6 Statistical analyses

Descriptive analyses were carried out using ANOVA, Student t-test or chi square test based on the variable characteristics. Brain measurements were found to be normally distributed based on graphs. The Univariate General Linear Model (GLM) was used to compare the brain volume of HC and ACC between: 1) currently depressed participants and healthy controls, 2) past MDE subjects and healthy controls, 3) currently depressed participants and past MDE subjects. We considered the following variables as potentially associated with brain size structures: gender, age, education level and total intracranial volume. We chose total intracranial volume instead of total brain volume because it seems to be more closely related to premorbid brain size (Davis, 1977; Pfefferbaum, 1994).

The interaction between HC and ACC volumes and gender on the main outcomes (currently depressed versus healthy subjects and past MDE versus healthy subjects) was tested. We have included in the models: gender, brain volumes and the interaction between gender and brain volumes. In the case of the presence of interaction ($p \leq 0.01$), we planned to perform stratified analyses in males and females.

All p-values were 2-tailed, and for primary analysis (ANOVA) the significance threshold was adjusted using the Benjamini-Hochberg false discovery rate (FDR) correction for multiple comparisons, in order to reduce false positive results ($q \leq 0.004$). Statistical analyses were performed using SPSS version 22.0 for Windows.

3. Results

3.1 Sample description

The mean age of participants was 71.25±4.06 years old. Sample description is shown in Table 1. Currently depressed individuals have a mean age at onset of 48.43±17.67 (n=68) and a mean number of lifetime depressive episodes of 2.01±2.07 (n=69). Past MDE subjects have an age at onset of 44.23±14.54 (n=79) and a mean number of lifetime depressive episodes of 1.80±3.86 (n=79). The two groups were not different on both age at onset (t=1.58, d.f.=145, p=0.12) and number of lifetime depressive episodes (t=0.42, d.f.=146, p=0.68). Sixty-six currently depressed individuals had a MINI diagnosis of depression.

Compared to healthy controls, female gender was over-represented among individuals with current or past MDE ($p<0.0001$ in all cases). Moreover, CESD-D total score was higher in both currently depressed individuals and past MDE subjects compared to healthy controls ($p<0.0001$ and $p=0.001$, respectively) and in currently depressed individuals compared to past MDE subjects ($p<0.0001$). Both total brain and total intracranial volumes were reduced in participants with current ($p=0.001$ and $p=0.001$, respectively) and past MDE ($p=0.02$ and $p=0.009$, respectively) in comparison to healthy controls. No further difference was found in socio-demographic or clinical features between the groups.

3.2 Current depression

Results are reported in Table 2. We found left posterior HC volume reduction in currently depressed individuals when compared to healthy ones ($F=10.84$, $p=0.001$) with manually measured HC. However, the difference between these two groups in both HC and ACC volumes was not significant by means of the automated method (FreeSurfer), see also Figure 2.

We performed supplementary analyses to further explore the reported significant association between the decrease in left posterior HC volume and current depression (manual method): i) we only included subjects with a MINI diagnosis of depression (n=66) ($F=3.93$, $p=0.048$); ii) we excluded subjects taking antidepressants (n=24) ($F=7.05$, $p=0.008$); iii) we excluded subjects with only current antidepressant treatment but without neither a MINI diagnosis of current MDE nor a CES-D score ≥16 (n=7) ($F=4.83$, $p=0.008$); iv) we added metabolic syndrome among covariates ($F=9.57$, $p=0.002$). In all these analyses the association remained.

3.3 Past MDE

Comparing individuals with past MDE versus those who never experienced depression, we found neither HC nor ACC volume reduction (Table 2 and Figure 2). No difference was reported even after comparing currently depressed individuals versus past MDE ones (even when only subjects with a MINI diagnosis of depression (n=66) were considered as currently depressed subjects).

3.4 Gender

We tested the interaction between both HC and ACC volumes and gender on both current depression and past MDE (versus healthy controls) but we did not find the presence of significant interaction. So we did not perform separate analyses for males and females.

4. Discussion

Our study investigated hippocampal (HC) and anterior cingulate cortex (ACC) volume differences occurring in depression in older adults of the general population. Our main finding is a left posterior HC volume reduction in currently depressed participants compared to healthy controls with manual HC measurement. When individuals with a history of past, but not current, MDE were compared to those who never experienced depression, no volume reduction was found in either the HC or ACC. A similar study reporting higher global brain atrophy (especially in HC and thalamus) in current MDD but not in past MDD has been recently performed (Geerlings, 2013). However, all their measures were automated and they did not correct for multiple comparisons. Moreover, when we slightly changed sub-group inclusion criteria (i. including only subjects with a MINI diagnosis of depression; ii. excluding subjects taking antidepressants; iii. excluding subjects with only current antidepressant treatment but without neither a MINI diagnosis of current MDE nor a CES-D score ≥16; iv. adding metabolic syndrome among covariates), the main result remained.

Hippocampus

Our findings are partly in line with previous studies supporting HC volume reduction in LLD (Agudelo, 2015; Andreescu, 2008; Ballmaier, 2008; Bell-McGinty, 2002; Benjamin, 2011; Egger, 2008; Lloyd, 2004; Steffens, 2000); however, in our study only the left posterior HC volume showed a significant reduction, probably due to the strict methodological adjustments we made to avoid type I errors. Neuropsychological studies have linked the alteration of HC in depression with impairments in memory (Hickie, 2005), executive functions (T. Frodl, 2006), but also motivation and emotion (Gray, 1983). Hence, reduced HC volume could play an important role in the pathophysiology of elderly depression by participating in affective symptoms and cognitive dysfunction that lie at the core of major depression (T. Frodl, 2006). Reduced HC volumes have also been associated with a longer course of illness in elderly depression (Bell-McGinty, 2002), but the extent to which volume reductions determine clinical outcome in MDD remains unknown. However, reduced HC volumes are not specific to depression. It has been observed in childhood trauma cohorts (Paquola, 2016) and in other psychiatric disorders (Geuze, 2005), such as schizophrenia, post-traumatic stress disorder,

borderline personality disorder and obsessive-compulsive disorder, but also in Alzheimer's disease (Jack, 1992), mild cognitive impairment and dementia (Geuze, 2005).

Importantly, only the manual method found differences in HC volumes. The strength of this method is its greater accuracy compared to automated methods (Boccardi, 2011). A study comparing manual volumetry to automated HC volumetry using FreeSurfer showed that, while FreeSurfer revealed good agreement with manual delineation in detecting HC atrophy, volume measured with this software could be 35% larger (Tae, 2008). Therefore, manual HC delineation represents the gold-standard helping in the detection of HC atrophy in Alzheimer's disease (Hsu, 2002; Lehmann, 2010; Morey, 2009; Mulder, 2014) and in chronic MDD (Tae, 2008). Manual measurement allows a precise segmentation of a structure that is still not univocally defined in imaging studies (different delineation protocols are still being used in studies analyzing HC) (Konrad, 2009).

Our results are consistent with studies reporting a volume reduction in the posterior HC section of adults suffering from depression (Maller, 2007; Neumeister, 2005; Sivakumar, 2015). Furthermore, studies indicate greater atrophy in the left HC of depressed individuals (Bremner, 2000; Y. I. Sheline, 1996; Yvette I. Sheline, 1999). Dysfunction in the posterior HC could lead to neurocognitive deficits implicating spatial learning and memory (Moser, 1993) impairments that have been highlighted in a neurocognitive study in non-medicated symptomatic depressed individuals (Porter, 2003). As for left posterior HC, a recent MRI study showed a significantly smaller left posterior HC in individuals suffering late onset depression versus controls (Sivakumar, 2015). This could suggest that measuring total HC volume without considering its sub-fields is less relevant in the analysis of HC volume changes in depression (Huang, 2013; Sivakumar, 2015). Eventually, our findings could be linked to the hypothesis based on stress-induced decreases in HC neurogenesis (Jacobs, 2000). However, HC volumetric reductions might also be due to changes in neuropil, glial number, and/or dendritic complexity (Pilar-Cuéllar, 2013). The evidence binding a decrease in HC cell proliferation with the pathogenesis of depression is mainly based on neuroimaging and postmortem studies (Miller, 2015) and further functional neuroimaging studies are needed to establish this potential link.

HC volumetric changes are influenced by factors such as medication effects (Maller, 2007; Schmaal, 2015). Since antidepressants suppress the toxic effects of stress on the HC and

increase HC neurogenesis (T. S. Frodl, 2008), we controlled the effect of antidepressant treatment. The decrease in left posterior HC volume in current depression remained even when subjects taking antidepressants were excluded from the analyses. Similarly, when we excluded subjects with only current antidepressant treatment but without neither a MINI diagnosis of current MDE nor a CES-D score ≥16, the result remained. We are aware that the inclusion criteria we chose have an important limitation, because current antidepressant treatment cannot be considered as a safe marker of current depression. However, excluding persons treated for depression could be problematic as well: treated persons are likely to have more severe symptomatology so excluding them could mean eliminate important information and significantly weaken the association. The dilemma is that persons treated for depression will have had their symptoms artificially lowered, but they would still have been exposed to the underlying biological changes and their anatomical correlates.

Neuroplasticity theory assumes that neural circuits and connections undergo lifelong modifications and reorganization in response to external or internal environmental stimuli. Adult neurogenesis involves precursors of cell proliferation, migration and differentiation mainly occurring in the dentate gyrus of the HC, therefore generating new neurons throughout life (Serafini, 2012). Sensitivity to stress is related to affective disorders (Swaab, 2005), and a disruption in the stress-axis increases levels of cortisol (Bao, 2008; Swaab, 2005) that consecutively seem to disable neurogenesis in HC and affect its volume (Koolschijn, 2009; Sapolsky, 2000; Sapolsky, 1986). Stress-induced reduction in neurogenesis may be an important factor in precipitating episodes of depression with recovery from depression requiring a restoration of the original basal rate of neurogenesis (whether it is due to antidepressant treatment or endogenous changes).

Anterior cingulate cortex

Our results on ACC were inconsistent with previous literature since only a few studies did not find any volume reduction in the ACC of depressed patients compared to controls (Bremner, 2002). In depression, a functional disruption of ACC may lead to an impaired initiation and organization of behavior (Devinsky, 1995). Thus, alterations in anterior cingulate could be associated with executive and psychomotor symptoms (Devinsky, 1995), often prominent in geriatric depression (Jose, 2001). These abnormalities could act as a predisposing factor rather than a cause to depression (George S. Alexopoulos, 2008) and the atrophy of dorsal and

rostral ACC could favor a chronic course of LLD (Gunning, 2009). Moreover, a recent meta-analysis reported that LLD tended to be associated with smaller volumes in circumscribed frontal and subcortical structures, with the most robust differences being found in thalamic volume (Bora, 2012). The lack of reported volume reduction could be linked to our conservative approach (FDR correction): in fact, without applying the FRD correction, we would be able to detect a lower right caudal ACC volume in currently depressed versus past MDE individuals (p=0.01).

Strengths and limitations

This paper has some consistent strengths. Our study is one of the very few that evaluated the association between lifetime depression and brain volume differences using MRI in a large community based older adults' sample (n=516). We focused on the two brain regions most consistently associated with volume reductions in depression and used two types of measurement for the HC: automated and manual (in particular, the fact that we also manually segmented the HC is a major strength of the study as it is the gold standard). We reduced selection bias and information bias using structured interviews and excluding participants with dementia. Furthermore, we used a highly conservative approach (FDR correction), not applied in the majority of previous studies, even if our analyses were mainly confirmatory and not explorative. Due to the design of our study we were able to consider current and past MDE. The most important confounders were taken into account. Hence, even if the association between depression and reduced hippocampal volumes is well established, this study reported that the reduction was isolated to the left posterior hippocampus; moreover, this finding validates earlier studies with smaller samples and without FDR correction.

Limitations should be recognized as well: 1) We did not have any information on the length and severity of the episodes nor on the duration of treatment, which are factors known to influence cerebral volume changes. Moreover, the course of depression at the time of assessment was not known. Finally, we could not consider the number of suicidal attempts, the lifetime history of electroconvulsive therapy, the lifetime use of lithium and antidepressants and their dosage, all factors influencing brain volumes. 2) The study is cross-sectional so it is only possible to establish co-occurrence and not causality. In particular, individuals with past MDE might never have had smaller HC volumes, so our hypothesis of a HC volume recovery would need to be verified in a longitudinal setting. 3) While we have adjusted for a number of correlates of HC volume change, the possibility that other clinical

and life-style factors may have confounded the association remains. For example, it cannot be excluded that the reduced left posterior HC volume, found in currently depressed participants and not in past MDE ones, could be due to age atrophy that leads to depression. 4) We reported no difference surviving FDR correction when we compared currently depressed versus past MDE individuals; however, not considering FDR correction, a small difference was present (p=0.03); 5) The scanner used (1.5 T GE Signa) is quite old, however it still generated excellent quality data; 6) Even if the sample is large, the size of some groups is small (e.g., past MDE subjects n=79).

5. Conclusions

Left posterior HC volume reduction was reported in subjects with late life depression but not in subjects with past MDE compared to healthy controls. This could be linked to brain neuroplasticity. Furthermore, this volume reduction has been detected only when the HC was measured using the manual method. This could indicate that the actual accuracy of automated methods did not yet match that of the manual one. Future large studies using newer versions of FreeSurfer would be interesting. It would be stimulating in the future to have prospective imaging studies investigating the severity of MDE and its evolution in depressed older adults.

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Figures

Figure 1. Flow chart of the inclusion/exclusion process of participants (MRI: magnetic resonance imaging; MINI: Mini International Neuropsychiatric Interview; MDE: major depressive episode). They have been included: currently depressed subjects (n=150), subjects with a past lifetime history of major depressive episode (n=79), and healthy controls (n=287).

Figure 2. Hippocampal volumes (both FreeSurfer and manual method) in the three groups: currently depressed subjects, subjects with a past lifetime history of major depressive episode, and healthy controls (MDE: major depressive episode; *: p=0.001). Current depression was associated with a lower left posterior hippocampal volume using manual measurement. Gender, age, education level, and total intracranial volume have been considered as covariates in the analyses.

Socio-demographic and clinical variables	Healthy controls (n=287)	Currently depressed (n=150)	Past MDE (n=79)				Controls versus currently depressed			Controls versus past MDE			Currently depressed versus past MDE		
							t/χ2	d.f.	p	t/χ2	d.f.	p	t/χ2	d.f.	P
	n, % or mean±SD			F/χ2	d.f.	p									
Gender (males)	173, 60.3	52, 34.7	25, 31.6	36.42	2	<0.0001	25.87	1	<0.0001	20.45	1	<0.0001	0.21	1	0.65
Age (years)	71.26±4.17	71.63±3.93	70.49±3.86	2.02	2, 513	0.13	-0.88	435	0.38	1.48	364	0.14	2.09	227	0.04
Education (a)				8.34	6	0.21	6.21	3	0.10	3.49	3	0.32	0.92	3	0.82
None-Low	61, 21.3	39, 26.0	22, 28.2												

Moderate	80, 28.0	46, 30.7	25, 32.1												
High	52, 18.2	33, 22.0	13, 16.7												
Very high	93, 32.5	32, 21.3	18, 23.1												
Total brain volume (cm3) (b)	1037.50±103.28	1002.94±107.43	1007.24±83.74	6.60	2, 502	0.001	3.22	424	0.001	2.39	360	0.02	-0.31	220	0.76
Total intracranial volume (cm3) (b)	1227.47±127.71	1184.50±130.24	1186.46±101.68	7.15	2, 502	0.001	3.26	424	0.001	2.63	360	0.009	-0.12	220	0.91
MMSE (c)	27.59±1.74	27.31±1.94	27.86±1.65	2.58	2, 512	0.08	1.52	434	0.13	-1.23	363	0.22	-2.13	227	0.03
<26	33, 11.5	25, 16.7	10, 12.7	2.28	2	0.32	2.24	1	0.13	0.07	1	0.78	0.64	1	0.42
≥26	253, 88.5	125, 83.3	69, 87.3												
CES-D total score (d)	7.29±4.20	22.38±8.04	9.12±3.90	373.08	2, 510	<0.0001	-25.73	433	<0.0001	-3.46	361	0.001	13.74	226	<0.0001
Anxiety disorders	0, 0.0	42, 28.0	31, 39.2	-	-	-							3.01	1	0.08

(MINI) (e)															
Metabolic Syndrome (f)	46, 17.2	34, 24.1	13, 17.1	3.13	2	0.21	2.84	1	0.09	0.01	1	0.99	1.43	1	0.23
Chronic Disorders (g)	141, 50.0	85, 58.2	39, 50.6	2.73	2	0.26	2.61	1	0.11	0.10	1	0.92	1.17	1	0.28

Table 1. Socio-demographic and clinical features of the sample (MDE: major depressive episode; MMSE: Mini Mental State Examination; CES-D: Centre for Epidemiologic Studies - Depression Scale; MINI: Mini International Neuropsychiatric Interview).

(a) Missing: controls=1, currently depressed=0, past MDE=1.

(b) Missing: controls=4, currently depressed=7, past MDE=0.

(c) Missing: controls=1, currently depressed=0, past MDE=0.

(d) Missing: controls=2, currently depressed=0, past MDE=1.

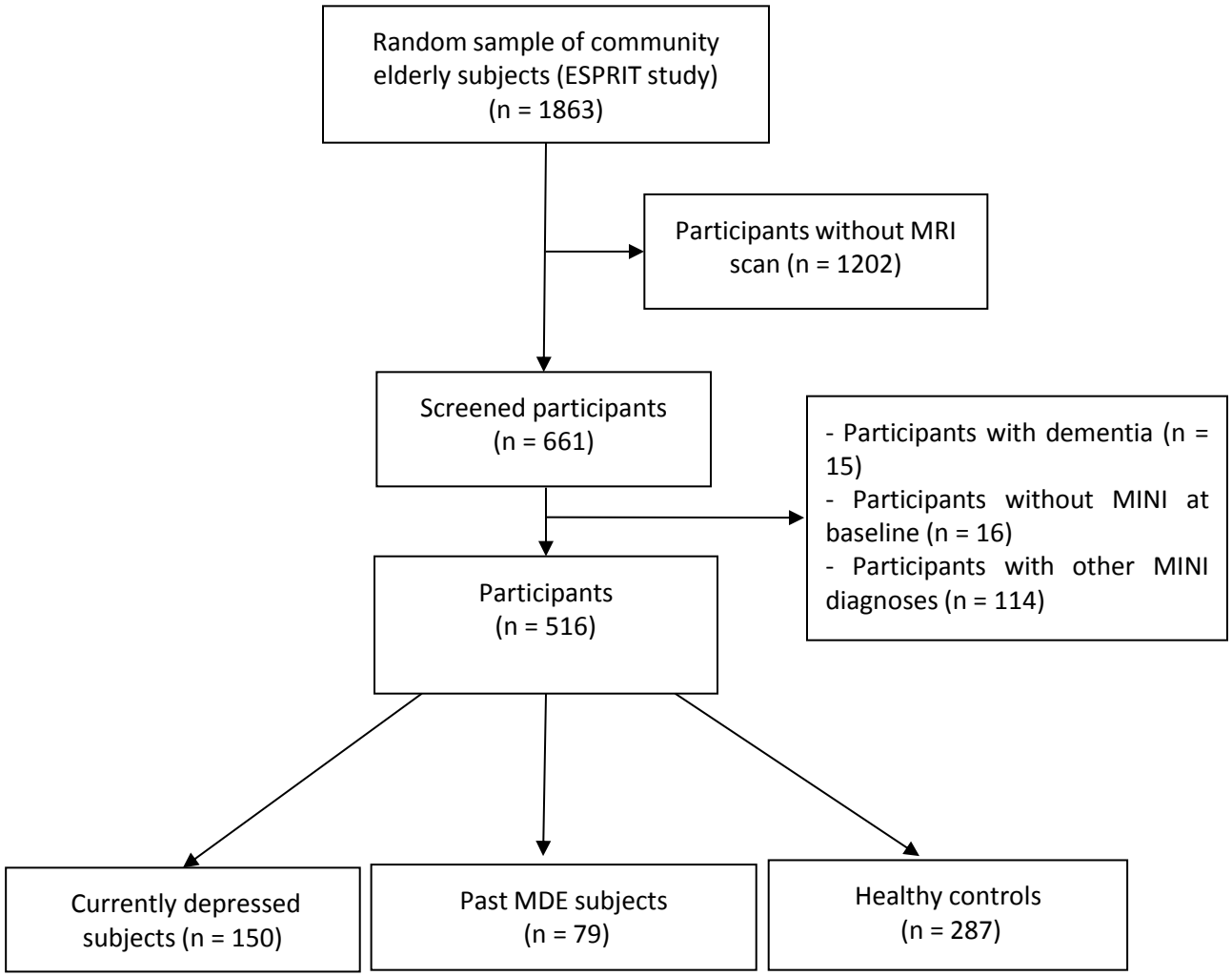
(e) Missing: controls=1, currently depressed=0, past MDE=0.

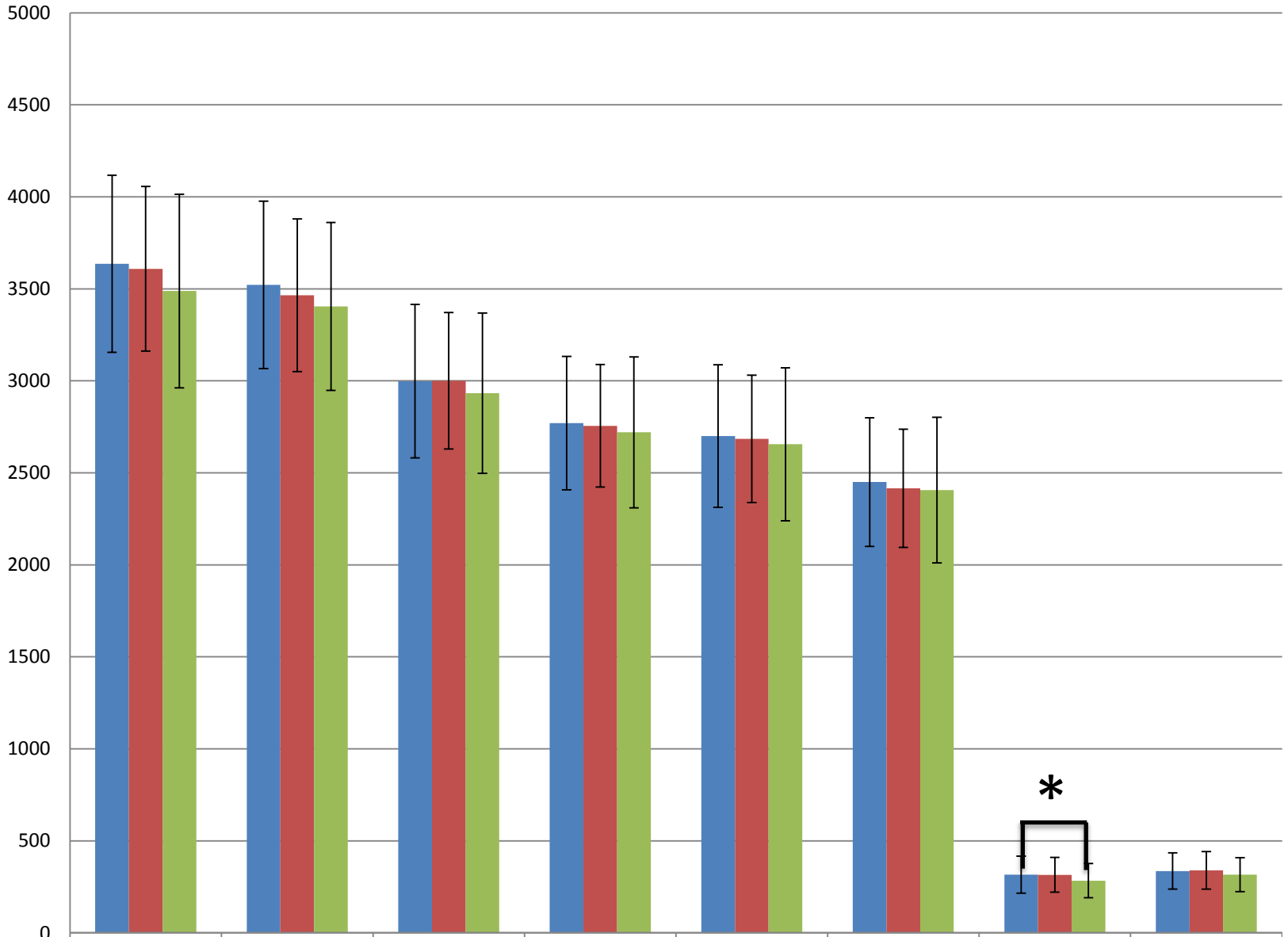
(f) Missing: controls=19, currently depressed=9, past MDE=3.

(g) Missing: controls=5, currently depressed=4, past MDE=2.

Cortical ROIs	Hemisphere	Volume (mm^3±SD)			ANOVA		Post hoc analyses					
					F	p	F	p	F	p	F	p
		Healthy controls (n=287)	Currently depressed (n=150)	Past MDE (n=79)			Controls versus currently depressed		Controls versus past MDE		Currently depressed versus past MDE	
Total hippocampus (FreeSurfer)	L	3635.76±487.79	3488.03±525.94	3608.93±447.19	0.96	0.38	1.53	0.22	0.01	0.96	1.05	0.31
	R	3521.79±461.50	3405.16±456.33	3464.65±414.94	0.44	0.65	0.61	0.43	0.28	0.60	0.01	0.93
Anterior hippocampus (Manual method)	L	2699.69±386.87	2655.52±415.55	2685.21±346.21	0.45	0.64	0.73	0.39	0.59	0.44	0.05	0.82
	R	2449.81±352.07	2406.12±395.41	2416.18±321.03	0.26	0.77	0.62	0.43	0.15	0.70	0.03	0.86
Posterior hippocampus (Manual method)	L	315.95±101.49	283.48±92.68	315.30±95.05	5.63	0.004*	10.84	0.001	0.16	0.69	4.94	0.03
	R	335.72±98.94	316.39±92.22	339.23±102.31	2.18	0.11	4.33	0.04	0.01	0.91	1.70	0.19
Total hippocampus (Manual method)	L	2998.24±416.87	2933.24±435.45	3000.52±370.35	0.43	0.65	0.02	0.89	0.66	0.42	0.68	0.41
	R	2769.90±362.06	2720.59±410.23	2755.40±333.16	0.17	0.84	0.19	0.66	0.29	0.59	0.03	0.86
Rostral anterior cingulate cortex	L	1747.90±423.19	1649.23±382.29	1644.80±340.74	0.13	0.88	0.16	0.69	0.01	0.96	0.03	0.87
	R	1696.97±449.69	1659.22±477.45	1699.85±497.43	1.86	0.16	1.36	0.24	2.65	0.10	0.72	0.40
Caudal anterior cingulate cortex	L	1586.83±381.66	1515.83±366.84	1599.08±388.80	1.15	0.32	0.53	0.46	1.15	0.28	2.17	0.14
	R	1464.51±408.23	1404.53±365.67	1524.89±381.73	2.75	0.06	0.63	0.43	3.09	0.08	6.40	0.01

Table 2. Cortical regions of interest in currently depressed subjects, past major depressive episode subjects and controls (ROI: regions of interest; MDE: major depressive episode; R: right; L: left). The following variables have been considered as covariates in the analyses: gender, age, education level, and total intracranial volume. *: the ANOVA significance threshold was adjusted using the Benjamini-Hochberg false discovery rate (FDR) ($q \leq 0.004$).


Random sample of community elderly subjects (ESPRIT study) (n = 1863)
Participants without MRI scan (n = 1202)
Screened participants (n = 661)
- Participants with dementia (n = 15)
- Participants without MINI at baseline (n = 16)
- Participants with other MINI diagnoses (n = 114)
Participants (n = 516)
Currently depressed subjects (n = 150)
Past MDE subjects (n = 79)
Healthy controls (n = 287)



	Total hippocampus (FreeSurfer) left	Total hippocampus (FreeSurfer) right	Total hippocampus (Manual method) left	Total hippocampus (Manual method) right	Anterior hippocampus (Manual method) left	Anterior hippocampus (Manual method) right	Posterior hippocampus (Manual method) left	Posterior hippocampus (Manual method) right
Controls	3635,76	3521,79	2998,24	2769,9	2699,69	2449,81	315,95	335,72
Past MDE subjects	3608,93	3464,65	3000,52	2755,4	2685,21	2416,18	315,3	339,23
Currently depressed subjects	3488,03	3405,16	2933,24	2720,59	2655,52	2406,12	283,48	316,39